ORIGINAL ARTICLE

Clinico-diagnostic experience with tuberculous lymphadenitis in Saudi Arabia

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Objective To describe the diagnosis and outcomes of tuberculous lymphadenitis in a low HIV-seroprevalence population at a hospital in Riyadh, Saudi Arabia.

Methods Retrospective case series of tuberculous lymphadenitis from 1983 to 1998 were examined.

Results There were 99 cases with a median age of 38 years and a female preponderance (female/male ratio of 1.3 : 1). Eighty per cent had cervical involvement and 36% had systemic symptoms. Eighty-nine per cent had their lymphadenopathy for more than 1 month. The diagnostic yield of tuberculin skin testing was 83%, of chest X-ray was 27%, of fine-needle aspiration was 46%, and of excisional lymph node biopsy was 97%. Only one-third of patients received a tuberculin test. There was no significant difference in outcome between 6 and 9 months of chemotherapy, and paradoxical enlargement of nodes occurred in only 6%.

Conclusions Tuberculous lymphadenitis in our study population was predominantly cervical in location. The diagnostic yield of FNA was lower than that reported in the literature, and might be improved by more frequent tuberculin skin testing, multiple aspirations of lymph nodes, or use of excisional biopsy as the initial diagnostic procedure. Most patients responded well to chemotherapy, with few complications.

Keywords Lymphadenitis, *Mycobacterium tuberculosis*, tuberculosis, Saudi Arabia

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INTRODUCTION

Lymphadenitis is the commonest form of extrapulmonary tuberculosis [1], and tuberculous lymphadenitis is among the commonest causes of peripheral lymphadenopathy in the developing world [2]. In developed countries, tuberculous lymphadenitis is usually a disease of the foreign-born [3–5], but in developing countries it is an endemic disease of young adults with a female preponderance [6].

Tuberculous lymphadenitis typically presents as painless, firm enlargement of the lymph nodes. The usual diagnostic tests are fine-needle aspiration (FNA) and/or excisional biopsy of a lymph node, although the diagnosis is sometimes established by the demonstration of concomitant pulmonary tuberculosis. It has been suggested that FNA should be the initial diagnostic test in developing countries with a high prevalence of tuberculosis because it is sufficiently sensitive and avoids the need for hospitalization and general anesthesia; however, excisional biopsy is preferred as the initial test in developed countries [2].

There are few reports of tuberculous lymphadenitis from the Middle East [7–10]. This report describes the presentation, diagnosis, and treatment of tuberculous lymphadenitis from 1983 to 1998 at a Saudi Arabian secondary- and tertiary-care hospital which serves a predominantly Bedouin population with low HIV seroprevalence.

MATERIALS AND METHODS

The King Fahad National Guard Hospital, a 500-bed facility situated in Riyadh, Saudi Arabia, provides secondary and tertiary care to National Guard soldiers and their dependents. Most National Guard soldiers are Bedouins and come from closely knit tribes and families. The HIV seroprevalence from July 1995 to December 1997 among 22 229 blood donors at the hospital was 0%; blood donors include soldiers and relatives of patients requiring blood products. Because of the extremely low prevalence of HIV infection in the referral population,

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HIV serology is not routinely done in patients diagnosed with tuberculosis. This is a report of a retrospective series of tuberculous lymphadenitis cases managed at the hospital from 1983 to 1998.

Cases were identified using the discharge diagnosis database from the Medical Records Department, a database of histology reports from the Pathology Department, and a database of positive *Mycobacterium tuberculosis* cultures from the Microbiology Laboratory. A confirmed case of tuberculous lymphadenitis was defined by a positive culture for *M. tuberculosis*, a positive acid-fast bacillus (AFB) smear, or the presence of caseating granulomas in histologic sections or cytologic smears with no clinical evidence of other infectious or non-infectious diseases. All lymph node biopsies were done by open excision. Some cases were diagnosed by incision and drainage of a caseous lymph node and AFB smear and culture of the pus. *M. tuberculosis* was cultured in Bactec broth and/or Lowenstein–Jensen agar and identified according to standard biochemical tests.

Charts were reviewed and the following data extracted: age, sex, presence of local or constitutional symptoms, body site of lymphadenitis, duration of lymph node enlargement, sites of extranodal involvement, chest radiologic findings, tuberculin skin test results, results of FNA and/or excisional lymph node biopsy, and details of antituberculous chemotherapy. The duration of lymph node enlargement was defined as acute (less than 1 month), subacute (1–3 months), or chronic (greater than 3 months). A tuberculin skin test induration size $\geqslant 10$ mm was considered to be a significant positive reaction. Long-term follow-up of treatment results was limited by the nomadic lifestyle of the study population.

All statistical analyses were generated using Stata version 4.0 (Stata Corporation, College Station, Tx, USA). The statistical significance of categorical variables was assessed by Fisher's exact test, and that of continuous variables was assessed by the two-sample Wilcoxon rank sum test.

RESULTS

Ninety-nine cases of tuberculous lymphadenitis were evaluated from 1983 to 1998. The mean number of cases per year was 6.2 and no temporal trend in incidence was observed. The sex and age distribution of cases is shown in Figure 1. There were 43 males and 56 females, and the median age was 38 years (range 1–78 years); five patients were less than or equal to age 12 years. The median age was not significantly different for males and females ($P = 0.73$). Ninety-six of the cases were Saudi nationals and three were Filipino nationals. Only one of the 99 cases was tested for HIV antibodies; this patient was seropositive and presented with concurrent tuberculous lymphadenitis and visceral leishmaniasis.

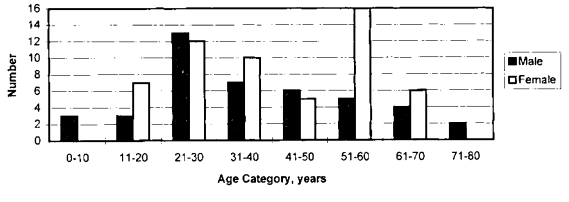

Figure 1 Tuberculous lymphadenitis cases by age and sex ($n = 99$).

The most frequent presentation of tuberculous lymphadenitis was sole involvement of the cervical lymph node region ($n = 63$). In addition, 16 patients had involvement at another site in addition to the neck (Table 1). Cervical involvement could be accompanied by axillary, intrathoracic, intra-abdominal, or inguinal lymphadenitis. Twenty other patients with lymphadenitis did not have cervical involvement (data not shown).

Ninety-eight of 99 (99%) patients had local symptoms or signs on presentation, and 36 of 99 (36%) had constitutional symptoms (fever, night sweats, weight loss). Lymph node enlargement was acute in six of 99 (11%) patients, subacute in 23 of 99 (23%) patients, and chronic in 27 of 99 (27%) patients. A sinus tract was observed in six cases.

The tuberculin skin test was significantly reactive ($\geqslant 10$ mm induration) in 29 of 35 (83%) patients tested. The chest radiograph was normal in 70 patients but revealed old fibrosis in four, parenchymal disease suggestive of tuberculosis in seven, and intrathoracic lymphadenopathy in 15 (Table 2). Four of seven patients with parenchymal abnormalities had *Mycobacterium tuberculosis* isolated from sputum, and one was culture positive from a lung biopsy.

The method of diagnosis in 99 cases of tuberculous lymphadenitis was as follows: positive excisional lymph node biopsy alone ($n = 57$), negative FNA but positive excisional lymph node biopsy ($n = 19$), positive FNA alone ($n = 15$), both positive FNA and excisional lymph node biopsy ($n = 1$), AFB-smear-positive lung biopsy ($n = 1$), AFB smear-positive and/or *M. tuberculosis* culture-positive sputum ($n = 4$), and AFB smear-positive and/or *M. tuberculosis* culture-positive caseous material obtained by incision and drainage at a lymph node site ($n = 2$).

Table 1 Presentations of tuberculous cervical lymphadenitis

Presentation	No.	%
Cervical, bilateral	9	11.4
Cervical, midline	4	5.1
Cervical, right	32	40.5
Cervical, left	4	17.7
Cervical, unspecified	4	5.1
Cervical + thoracic	13	16.4
Cervical + abdominal	1	1.3
Cervical + axillary + inguinal	1	1.3
Cervical + thoracic + abdominal	1	1.3
Total	79	100

Table 2 Chest radiographic findings in tuberculous lymphadenitis

Radiographic finding	No.	%
Normal	70	72.9
Fibrosis	4	4.2
Parenchymal disease[a]	7	7.3
Hilar/mediastinal/paratracheal nodes	15	15.6
Total	96	100

[a] Four patients had sputum and one patient had lung biopsy that was positive for acid-fast-bacilli and/or *M. tuberculosis*.

The yield of diagnostic tests in tuberculous lymphadenitis is shown in Table 3. Excisional lymph node biopsy was diagnostic in 76 of 78 (97%) cases, incision and drainage was diagnostic in two of two (100%) cases, and FNA was diagnostic in 16 of 35 (46%) cases. Among 35 cases receiving FNA, both AFB smear and tuberculosis culture were performed in 17, neither were performed (i.e. cytologic examination only) in 13, AFB smear only was performed in four, and tuberculosis culture only was performed in one. The yield of *M. tuberculosis* culture exceeded that of AFB smear for both FNA and excisional lymph node biopsy. Non-tuberculous mycobacteria were not isolated. Antimicrobial susceptibility was available for *M. tuberculosis* isolates in 27 patients; no isolates exhibited primary resistance to first-line antituberculous drugs.

All 99 cases of tuberculous lymphadenitis received antituberculous chemotherapy. Eighteen patients received two drugs, 67 received three drugs, 13 received four drugs, and one received five drugs. Ninety-eight of 99 patients received an isoniazid–rifampin-containing regimen. Among 86 patients receiving isoniazid, 16 patients received at least 12 months of treatment, 52 received at least 9 months of treatment, and 73 received at least 6 months of treatment. The median duration of treatment with isoniazid was 9 months (range, 2–30 months; $n = 86$), with rifampin was 9 months (range, 2–30 months; $n = 85$), with pyrazinamide was 3 months (range, 2–30 months; $n = 49$), with ethambutol was 5.5 months (range, 1–12 months, $n = 32$), and with streptomycin was 1 month (range, 1–2 months; $n = 6$). There was no difference in cure rate among those who received 9 or more months of therapy and those who received 6 or more months but less than 9 months of therapy ($P = 1.00$). The overall treatment results in the 99 patients were as follows: 73 patients were cured, one patient relapsed, and 25 had incomplete follow-up. The patient who relapsed had been treated with isoniazid, rifampin, and pyrazinamide for 9 months but had a recurrence of a neck abscess; biopsy revealed chronic inflamed muscle and granulomatous inflammation of a lymph node with no AFB seen. This patient was restarted on antituberculous chemotherapy and cured by retreatment.

Table 3 Diagnostic tests in tuberculous lymphadenitis[a]

Procedure	No. positive	Total	% positive
Chest radiograph	26	96	27
Tuberculin skin test	29	35	83
Fine-needle aspirate			
Histology	11	35	31
AFB smear	7	21	33
TB culture	9	18	50
Excisional lymph node biopsy			
Histology	76	78	97
AFB smear	45	77	58
TB culture	38	61	62
Incision and drainage	2	2	100

[a] Some patients had more than one kind of diagnostic procedure.

Of 99 patients who were treated, six (6%) had enlargement of their lymph nodes after starting chemotherapy. Treatment outcomes in these patients with paradoxical enlargement included three cures, one bacteriologic relapse, and two patients with incomplete follow-up.

DISCUSSION

In this 16-year series of 99 patients with tuberculous lymphadenitis, no secular trend in incidence was observed. The patients were young with a median age of 38 years, and there was a slight preponderance of females (female/male ratio of 1.3 : 1), as noted in other studies [6,7,11]. Dandapat et al speculate that the female preponderance reflects a greater consciousness of their physical appearance which leads them to seek medical attention [6].

The most common clinical presentation of tuberculous lymphadenitis at our hospital was sole involvement of the cervical lymph nodes (63 of 99 patients, 64%), with the right side more frequently involved than the left side. Sixteen other patients had cervical lymphadenitis plus lymphadenitis at other sites, so, in total, 79 of 99 (80%) patients had cervical involvement. Other studies in developing countries have revealed the predominance of the cervical site, with a prevalence of neck involvement ranging from 65% to 89% [6,9,12]. Cervical lymphadenitis can arise when inhaled tubercle bacilli deposit in the tonsils or pharynx and spread by the lymphatics to the regional nodes [13]. Alternatively, pulmonary infection may be complicated by hematogenous seeding of cervical nodes [13]. Perhaps the existence of dual pathways of infection explains the predominance of the cervical location in tuberculous lymphadenitis.

The absence of constitutional symptoms does not make a diagnosis of tuberculous lymphadenitis less likely. Only 36% of our cases had constitutional symptoms, and in other studies the prevalence of constitutional symptoms ranges from 33% to 85% [6,11,14].

Only one-third of the patients received a skin test, of whom 83% had a significant reaction. In other studies, 74–96% of patients with tuberculous lymphadenitis had positive skin tests [4,6,7,14]. Thus, tuberculin skin testing was underutilized in the investigation of lymphadenitis at our hospital, despite its reasonable sensitivity, and this may have been due to the perception that such testing has less diagnostic value in a country with universal BCG vaccination in early childhood. However, tuberculin reaction size following BCG vaccination wanes with time, and should generally not confound the interpretation of a Mantoux test in adults [15] or children [16].

In a prospective study utilizing excisional biopsy as the diagnostic standard, Lau et al [17] observed that the diagnostic yield of FNA was considerably enhanced in the presence of a strong tuberculin skin test reaction. For FNA alone, the sensitivity was 77% and the specificity was 70%, but for the combination of FNA and Mantoux test, the sensitivity was 90% and the specificity was 84%. Since the diagnostic yield of FNA in our study was relatively low (see below), the addition of Mantoux testing may allow more patients to be diagnosed without the need to proceed to excision biopsy.

Excisional lymph node biopsy had the highest diagnostic yield in this series (97%), and the majority of cases were diagnosed by excisional biopsy without antecedent FNA. Because this study was retrospective, it is difficult to determine why more patients did not initially receive FNA. Nonetheless, in 35 patients who had initial FNA of a lymph node, the diagnosis was established in only 16 (46%); this compares with an FNA diagnostic yield of 50–83% in other studies in developing countries [6,7,18]. In the 19 patients in whom FNA was not diagnostic, subsequent excisional biopsy established the diagnosis in 100%. Part of the reason for the disappointing yield of FNA may be the fact that less than half of all FNA specimens were processed for both AFB smear and tuberculosis culture, possibly because of an inadequate quantity of aspirated material. Failure to perform both tests will certainly reduce the diagnostic yield of FNA, because culture of FNA specimens is more sensitive than AFB smear for detecting *M. tuberculosis* [10,18–20]. In addition, FNA is more likely to introduce sampling error than excisional biopsy. The low yield of FNA at our hospital might be increased by obtaining multiple aspirations of the lymph nodes during FNA. It was not possible from the medical record review to determine how many aspirates were taken from each patient who received FNA.

Almost all patients were treated with a regimen containing at least isoniazid and rifampin, and the median duration of administration was 9 months for these agents. No significant difference in cure rate was observed between those patients who received at least 9 months of treatment and those who received at least 6 months but less than 9 months of treatment with isoniazid, rifampin, and another first-line drug. This result agrees with other studies that have shown equal effectiveness of 9-month and 6-month regimens in the treatment of tuberculous lymphadenitis [21–23].

Paradoxical enlargement or appearance of new lesions has been described during the treatment of brain tuberculomas [24,25] and tuberculous lymphadenitis [21]. The incidence of paradoxical enlargement or new lymph node development varies from 10% to 23% [12,26], and is thought to represent hypersensitivity to tuberculoprotein rather than bacteriologic relapse. Management of paradoxical lymph node enlargement can include observation, corticosteroid administration, or surgical excision. Only 6% of patients in the present study had paradoxical enlargement of nodes during or after chemotherapy, and only one of these patients had a bacteriologic relapse. No primary drug resistance was encountered in the patients tested.

Mediastinal lymphadenopathy was observed in 9% of our cases, and in developed countries is likely to raise the possibility of malignant lymphoma. However, in developing countries, tuberculosis is a more common cause of mediastinal lymphadenopathy, and if mediastinoscopy is not available and no other lymph nodes can be easily biopsied, then a trial of empirical antituberculous therapy is justified. Reduction of mediastinal lymph node size after 2–3 months of antituberculous treatment supports the diagnosis and eliminates the need to perform mediastinoscopy.

In conclusion, mycobacterial lymphadenitis in this study was predominantly caused by *M. tuberculosis* sensitive to first-line antituberculous drugs. Cervical and intrathoracic lymph nodes were commonly involved and the minority of patients had constitutional symptoms. Excisional biopsy was superior to FNA for diagnosis. A good therapeutic response with a low frequency of complications was seen with 6- and 9-month treatment regimens.

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